Angiogenesis in Hematologic Malignancies

Essay
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Presented by

Marwa Salah Farhan
M.B.,B.Ch.

Under supervision of

Prof. Dr. Hanaa Hamed Arnaaot
Professor of Clinical Pathology
Cairo University

Dr. Noha Mohamed Hosny Shahin
Lecturer of Clinical Pathology
Cairo University

Faculty Of Medicine
Cairo University
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Abstract

Increased angiogenesis is important in the pathophysiology of solid tumors as well as haematological malignancies. Different angiogenic factors were found to cause increased angiogenesis. By measuring these factors in patients of haematological malignancies, they were found to be increased compared to normal controls.This led to increased angiogenesis in the bone marrow of these patients.

These facts can be used in the prognosis of haematological malignancies.

Antiangiogenic agents can be used in the treatment of these patients, which decreases the doses of chemotherapy.

Key Words:

Angiogenesis, Leukemia, Antiangiogenic therapy.

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Contents

List of abbreviations

AAV	adeno-associated virus
aFGF	acidic fibroblast growth factor
AML	acute myeloid leukemia
Ang	angiopoietin
APL	acute promyelocytic leukemia
As2O3	arsenic trioxide
ATRA	all-*trans* retinoic acid
bFGF	basic fibroblast growth factor
BMSCs	bone marrow stromal cells
BrdU	bromodeoxyuridine
CAM	chorioallantoic membrane
CEPs	circulating endothelial precursor cells
CLL	chronic lymphocytic leukemia
CM	conditioned media
CML	chronic myelogenous leukemia
CMPDs	chronic myeloproliferative disorders
COX-2	cyclooxygenase-2
CR	complete remission
EC	endothelial cell
EGF	epidermal growth factor
eNOS	endothelial nitric oxide synthase
EPC	endothelial progenitor cell
FAB	French-American-British
Flt-1	fms-like tyrosine kinase-1
G-CSF	granulocyte colony stimulating factor
GFP	green fluorescent protein
GLUT	glucose transporter
GMA	glycol-methacrylate
GM-CSF	granulocyte-macrophage colony stimulating factor
HCC	hepatocellular carcinoma
HGF	hepatocyte growth factor
HIF	hypoxia inducible factor
HMCLs	human myelomacell lines
HSV-1s	herpes simplex-1 viruses
HUVECs	human umbilical vein endothelial cells
IFN	interferon
IL	interleukin

IMiD	immune modulatory drug
JNK	junctional N-terminal kinase
KDR	kinase insert domain-containing receptor
LAP	latency-associated peptide
MDS	myelodysplastic syndrome
mg/kg	milligram per kilogram
MLV	murine leukemia virus
mm	millimeters
MM	multiple myeloma
MMM	myelofibrosis with myeloid metaplasia
MMP	matrix metalloproteinase
MVD	microvascular density
ng/mL	nanogram per milliliter
NC1	nontriple helical C-terminal
NK	natural killer
PAI	plasminogen activator inhibitor
PC	prostate carcinoma
PCLI	plasma cell labeling index
PCNA	proliferating cell nuclear antigen
PCR	polymerase chain reaction
PDE	phosphodiesterase
PDGF	platelet-derived growth factor
PlGF	placenta growth factor
RARα	retinoic acid receptor alpha
RT-PCR	reverse transcription-polymerase chain reaction
SCID	severe combined immunodeficiency
SiRNA	small interfering RNA
TGF	transforming growth factor
tk	thymidine kinase
TLL	T-cell lymphoma leukemia
TNP-470	Takeda neoplastic product-470
TSP/THBS	thrombospondin
tum	tumastatin
uPA	urokinase-like plasminogen activator
VEGF	vascular endothelial growth factor
VEGFR	vascular endothelial growth factor receptor
VHL	von Hippel Lindau
VPF	vascular permeability factor
vWF	von Willebrand factor
WM	Waldenstrom's macroglobinemia

μm	micrometer

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Introduction

Angiogenesis is defined as the production of new blood vessels from an existing vascular network. It consists of a stepwise process of activation of existing endothelial cells, degradation of the extracellular matrix (ECM), and proliferation and migration of endothelial cells toward the angiogenic stimulus. Degradation of the ECM components by matrix metalloproteinases (MMPs) allows the migrating cells to invade along a front and organize themselves into a three-dimensional matrix . Subsequently, vessel patency is established when intra- and intercellular vacuoles coalesce.

Angiogenesis is important in a variety of physiologic and pathologic disorders. It is a central element in embryogenesis, ovulation, wound healing, diabetic retinopathy, and rheumatoid arthritis and in the establishment and spread of malignant tumors. Angiogenic factors include direct angiogens, indirect angiogens, and integrins. Direct angiogens stimulate the formation of new blood vessels directly. Indirect angiogens promote neovascular formation by paracrine stimulation of direct angiogens. Integrins mediate interactions between the developing vessels and components of the extracellular matrix**.**

Tumors can exist for months or years without neovascularization. However, with clonal progression, subsets of the tumor population may undergo a switch to an angiogenic phenotype. This switch involves a change in the local balance between pro- and antiangiogenic factors. Clones of the tumor with a proangiogenic phenotype may produce their own angiogenic growth factors, mobilize angiogenic substances from the ECM, and recruit host cells such as monocytes/macrophages to produce angiogenic molecules**.**

Recently, however, it has become clear that angiogenic factors play an important role in the pathophysiology of lymphocytic and myelogenous leukemias, myelodysplastic syndromes, myeloproliferative diseases, multiple myeloma, and non-Hodgkin's lymphomas**.**

The endothelial cell proliferation and microvessel formation are regulated by a wide range of soluble mediators, including angiogenin,angiopoietin-1, angiopoietin-2, basic fibroblast growth factors, vascular endothelial growth factor (VEGF), VEGF-D, angiostatin and endostatin.This correlates with clinical characteristics in leukemia and non-Hodgkin's-lymphoma and the serum/plasma concentrations serve as predictors of poor prognosis**.**

Vascular endothelial growth factor (VEGF) is a principal direct angiogen. By binding to 1 of 3 receptors (VEGFR-1, -2, or -3), it influences vasculogenesis during embryogenesis, physiologic and neoplastic angiogenesis, and lymphangiogenesis. Evidence now suggests that VEGF has a major role in the development and progression of hematologic malignancies such as acute leukemia, chronic leukemia, myelodysplasia, non-Hodgkin's lymphoma, and multiple myeloma. Potential therapeutic interventions to interrupt the VEGF signaling pathway of malignancy include antibodies that neutralize the growth factor and small molecules that inhibit the receptor tyrosine kinase activity of VEGF receptors**.**

Aim Of Work:

To explore the role of angiogenesis in haematologic malignancies and its relationship with the progression of acute and chronic leukemia.Recent applications of anti-angiogenic agents which interfere with or block leukemia will be reviewed.

Factors Affecting Angiogenesis

Angiogenesis (angio'gen'esis) - the growth of new blood vessels - is an important natural process occurring in the body, both in health and in disease.

The process of angiogenesis occurs as an orderly series of events where diseased or injured tissues produce and release angiogenic growth factors (proteins) that diffuse into the nearby tissues ***(Madri et al.,1996).***

The angiogenic growth factors bind to specific receptors located on the endothelial cells (EC) of nearby preexisting blood vessels. Once growth factors bind to their receptors, the endothelial cells become activated. Signals are sent from the cell's surface to the nucleus. The endothelial cell's machinery begins to produce new molecules including enzymes ***(Rosen, 2002).***

Enzymes dissolve tiny holes in the sheath-like covering (basement membrane) surrounding all existing blood vessels

The endothelial cells begin to divide (proliferate), and they migrate out through the dissolved holes of the existing vessel towards the diseased tissue (tumor)**.** Specialized molecules called adhesion molecules, or integrins (avb3, avb5) serve as hooks to help pull the sprouting new blood vessel sprout forward .

Additional enzymes (matrix metalloproteinases, or MMP) are produced to dissolve the tissue in front of the sprouting vessel tip in order to accommodate it. As the vessel extends, the tissue is remolded around the vessel.

Angiogenesis is active during development but is relatively quiescent during normal adult life. The process can be resumed after tissue injury, for example, but is otherwise thought not to undergo constant change.